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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,174	11/14/2001	Mario Anthony Moscarello	2132.024	6896

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EXAMINER	
COUNTS, GARY W	
ART UNIT	PAPER NUMBER
1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/992,174	MOSCARELLO ET AL.	
	Examiner	Art Unit	
	Gary W. Counts	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06/21/05 & 06/01/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *06/01/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the claims

This office action is in response to the Granted petition decision (06/21/05) to revive the application. The amendment filed June 1, 2004 is acknowledged and has been entered.

Specification

1. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 22—26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing multiple sclerosis by determining a level of anti-MBP IgG or a combination of anti-MBP IgG and anti-MBP IgM , does not reasonably provide enablement for diagnosing multiple sclerosis by determining only a level of anti-MBP IgM. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. The factors that must be considered in determining

undue experimentation are set forth in *In re Wands* USPTQ2d 14000. Factors to be considered in determining whether a disclosure would require undue experimentation include (1) the nature of the invention, (2) the state of the prior art, (3) the predictability or lack thereof in the art, (4) the amount of direction or guidance present, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the relative skill of those in the art, and (8) the breadth of the claims.

The instantly recited claims are directed to a method of diagnosing multiple sclerosis in a mammal consisting of the steps of (a) obtaining a sample of body fluid from the mammal, wherein the body fluid includes, blood, blood products and saliva, (b) performing an enzyme-linked immunosorbent assay (ELISA) which binds myelin basic protein and characterized by utilizing heparin to reduce non-specific charge interactions with MBP, thereby increasing sensitivity of the assay to about 77%; (c) determining a level of at least one autoantibody selected from the group consisting of anti-MBP IgG, anti-MBP IgM and a mixture thereof specific for said at least one autoantibody in said sample; and (d) comparing said level of said at least one autoantibody, wherein said level is statistically significant, whereby a diagnosis or monitoring of MS in said mammal is made with a specificity of about 95% and a likelihood ratio (LR) value of about 14.8.

The specification on page 26, lines 10-13 discloses that measurement of plasma MBP autoantibodies (IgG) by enzyme-linked immunosorbent assay (ELISA) is effective in achieving the clinical objectives of high sensitivity (77%) and specificity (95%). Voumvourakis et al., (Greek Microbiology Organization Newsletter 37, 666-672) discloses on page 668 that only patients with the IgG and IgA isotypes showed antibody

levels of a statistically significant difference when compared to a control group. Further, applicants specification on page 27 discloses that no definitive feature of the patients with elevated anti-MBP IgM could be ascertained. Page 28, lines 7-9 discloses that IgM may prove useful as an indicator of an initial episode or in predicting disease progression. Thus, the specification does not show that IgM as a sole marker can be used for the positive diagnosis of multiple sclerosis. There are no working examples provided in the specification providing guidance or evidence for diagnosing multiple sclerosis by determining only the level of anti-MBP IgM. A best a diagnosis of multiple sclerosis can be performed by determining a level of anti-MBP IgG or a combination of anti-MBP IgG and anti-MBP IgM and comparing to a control. Thus, one skilled in the art cannot practice the invention without undue experimentation, because in order to a high level of predictability that anti-MBP IgM provides for a diagnosis of multiple sclerosis and as shown by the prior art and applicants own disclosure. IgM does not provide statistically significant levels for diagnosis of multiple sclerosis.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 22-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 22 is vague and indefinite because it recites a method for diagnosing or monitoring multiple sclerosis. It is unclear which is being done. Further, diagnosing would involve a definitive yes or no for having the disease, whereas monitoring would

involve determining a progression and would also require samples taken at different time intervals. Therefore, it is unclear how both are performed.

Claim 22 the recitation "blood products" is vague and indefinite. There is no definition provided for the term and it is unclear what the term encompasses. Does anything made of blood or containing blood include a blood product? Does applicant intend only something within blood? It is recommended to delete the term from the claim and replace with --serum or plasma--. Applicant is reminded that limitations from the specification are not read into the claims.

Claim 22 the recitation "about" is a relative term which renders the claim indefinite. The term "about" is not defined by the claim, the specification does not provide a definition for the term. The specification on page 26, lines 10 – 12 discloses "the clinical objectives of high sensitivity (77%). See other deficiencies within the claims directed to the term "about".

Claim 22, line 5 is vague and indefinite because it is unclear if applicant intends that the body fluid further includes blood, blood products and saliva (i.e. a traumatic lumbar puncture wherein the cerebrospinal fluid would also include blood) or if the body fluid is one of the fluids selected from blood, blood products and saliva. The specification on page 33, line 20 discloses that the body fluid is blood or blood products. If applicant intends that the body fluid is blood, blood products or saliva. It is recommend to amend the claim to clearly recite this and to place the body fluid in a proper Markush recitation. Applicant is reminded that limitations from the specification are not read into the claims.

Claim 22 is vague and indefinite because it is unclear what applicant is detecting. Step (b) appears to be an assay for binding myelin basic protein. Further, it is unclear how an assay binds myelin basic protein. Does applicant intend performing an ELISA wherein an antibody is immobilized to capture myelin basic protein or does applicant intend that an ELISA is perform wherein immobilized myelin basic protein captures something or does applicant intend something else? Step (c) appears to be determining a level of one autoantibody and step (d) only recites comparing autoantibody. It is unclear what relationship exits between steps b and c and how is step b (which appears to be determining MBP) used in step (d)?

Claim 22 step (c), lines 13-14 "the recitation specific for said at least one autoantibody in said sample" is vague and indefinite. It is unclear what applicant is doing. How is the at least one autoantibody specific for the at least one autoantibody in the sample? Please clarify.

Claim 22 step (d) is vague and indefinite because it is unclear what applicant is comparing the level of autoantibody to. Is applicant comparing the level to the myelin basic protein of step (b)? Is applicant comparing the level to a level obtained from a diseased patient? Is applicant comparing the level to a baseline or standard? Is applicant comparing the level to a level of a healthy patient?

Claim 24 is vague and indefinite because it is unclear how a method of monitoring is performed on a single sample. It appears that monitoring a disease would require obtaining different samples at different times and comparing the levels to each other to monitor a disease.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 22-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voumvourakis et al (Detection of anti-MBP in the serum of patients with multiple sclerosis, Greek Microbiology Organization Newsletter (1992) 37, 666-672) in view of

Pesce et al (Cationic antigens Problems associated with measurement by ELISA, Journal of Immunological methods, 87 (1986) 21-27).

Voumvourakis et al disclose a method wherein a serum sample is obtained from an MS patient. Voumvourakis et al discloses that the sample is subjected to an ELISA assay wherein an immobilized myelin basic protein (MBP) (cationic protein) is used to capture and determine levels of anti-MBP IgG and anti-MBP IgM. Voumvourakis et al discloses that the determined levels are compared to healthy controls (p. 668) and statistically significant levels are determined for the IgG antibodies.

Voumvourakis et al differ from the instant invention in failing to teach the utilization of heparin to reduce non-specific charge interactions with MBP.

Pesce et al disclose the use of heparin to reduce non-specific charge interactions of cationic proteins that plague the sensitivities of ELISAs. Pesce et al disclose that non-specific reactivity of the cationic protein could almost completely be eliminated by carrying out the antibody-antigen incubation in the presence of heparin (p. 23) and further discloses that the use of heparin allows for the enhancement of antigen-antibody reactions because of neutralization of the positive charges on the antigen (p. 27).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the use of heparin as taught by Pesce et al into the method of Voumvourakis et al because Pesce et al shows that non-specific reactivity of the cationic protein (MBP is cationic) can almost completely be eliminated by carrying out the antibody-antigen incubation in the presence of heparin and further discloses that

the use of heparin allows for the enhancement of antigen-antibody reactions because of neutralization of the positive charges on the antigen. Therefore, one of ordinary skill in the art would have a reasonable expectation of success incorporating heparin as taught by Pesce et al into the method of Voumvourakis et al.

Also, claim 22 recites an interpretive "whereby" clause. Claim 22 states: "whereby a diagnosis or monitoring of MS in said mammal is made with a specificity of about 95% and a likelihood ratio (LR) value of about 14.8".

Regarding the interpretive "whereby" clause as recited in claim 22, it is noted that such interpretive clauses do not recite any additional active method steps, but simply state a characterization or conclusion of the results of those steps. Therefore, such "whereby" clauses are not found to further limit the method defined by the claims. See Texas Instruments, Inc. v. International Trade Comm., 988 F.2d 1165, 1171, 26 USPQ2d 1018, 1023 (Fed Cir. 1993)("A 'whereby' clause merely states the results of the limitations in the claim adds nothing to the patentability or substance of the claim."). See also Minton v. National Assoc. of Securities Dealers, Inc., 336 F.3d 1373, 1381, 67 USPQ2d 1614, 1620 (Fed. Cir. 2003)("A whereby clause in a method claim in not given weight when it simply expresses the intended results of a process step positively recited.").

With respect to the recitation "sensitivity of said assay to about 77%" and the recitation "specificity of about 95% and a likelihood ratio (LR) value of about 14.8". Since the combination of Voumvourakis et al and Pesce et al teach the same assay as

recited, the assay of Voumvourakis et al would have a sensitivity, specificity and likelihood ratio as recited.

10. Claims 25 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Voumvourakis et al and Pesce et al in view of Landry (5,736,343) or Bishop et al., (Clinical Chemistry 2nd edition, 1992, pages 70-71).

See above for the teachings of Voumvourakis et al and Pesce et al.

Voumvourakis et al and Pesce et al differ from the instant invention in failing to teach first and second samples obtained at different times.

Landry discloses that it is known in the art that for monitoring the course of a disease in a subject that first and second samples are taken at different time intervals and comparing the amounts determined in order to indicate the course of the disease (col 15).

Bishop et al discloses that it is known in the art for monitoring that a test result is compared with values previously obtained from the same patient (col 71).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate comparison steps to previously obtained values because both Landry and Bishop show that it is known in the art to compare values to previous obtained values in order to provide the monitoring of a disease. Thus, one or ordinary skill in the art would have a reasonable expectation of success comparing the values to previously obtained values to monitor the progression of a disease.

Response to Arguments

11. No claims are allowed.

12. Applicant's arguments with respect to claims 22-26 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary W. Counts whose telephone number is (571) 2720817. The examiner can normally be reached on M-F 8:00 - 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gary Counts
Examiner
Art unit 1641
March 30, 2007

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